REMARKS

Claims 6-13 are pending and under consideration in the current application. The Examiner has withdrawn claims 1-5 and 14-20 as being drawn to the non-elected invention.

Priority Claim

The Examiner alleges that the presently-claimed invention is only properly entitled to the priority claim to international application PCT/US02/27247, filed August 26, 2002. Applicants respectfully submit that the Examiner's determination is incorrect, and that the presently claimed invention is indeed entitled to the benefit of full priority to U.S. Provisional Patent Application No. 60/314,837, filed on August 24, 2001, for the following reasons.

Applicants note that MPEP § 201.11 states, "There are several conditions for a later-filed application to receive the benefit of the filing date of a prior-filed application under...35 U.S.C. 119(e)," including conditions such as copendency, explicit claim to priority, and disclosure of the invention, among other things. The Examiner only alleges that the claimed invention does not fully satisfy the requirements of written description and enablement, and therefore, Applicants take this as an indication that the Examiner acknowledges compliance with all other requirements set forth in MPEP § 201.11.

Regarding the Examiner's allegation that the claimed invention does not fully satisfy the requirements of written description and enablement, Applicants note that the Examiner has not provided any description of the alleged deficiency in the provisional patent application. Nonetheless, Applicants respectfully disagree with the Examiner's rejection of priority for the following reasons.

Applicants remind the Examiner that the MPEP sets the standard for the Examiner's burden in making a rejection based on an alleged lack of written description:

> A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the Examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of **presenting by a preponderance of evidence** why a person skilled in

> the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d at 263, 191 USPQ at 97. (emphasis added).

Applicants respectfully submit that the Examiner has not met this burden.

Applicants contend that they have indeed provided sufficient written description as required by the applicable law. In the landmark case of *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991), the Court of Appeals for the Federal Circuit traced the development of the written description requirement under 35 U.S.C. §112, first paragraph. The *Vas-Cath* Court, in a unanimous opinion, noted approvingly that in a written description analysis, "[t]he primary concern is factual and depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure." *Vas-Cath*, 19 USPQ2d at 1116 (quoting *In re Wertheim*, 191 USPQ 90, 96 (C.C.P.A. 1976)) (emphasis added). After discussing the policy reasons underlying the requirement, the Court set forth the standard for the written description requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use;" the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. . . . The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter."

Vas-Cath, 19 USPQ2d at 1117 (emphasis added) (quoting *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). Therefore, it is well-settled that the knowledge of those skilled in the art informs the written description inquiry.

Applicants submit that, at the time the present application was filed, the skill in the relevant art of angiogenesis and inflammation was indeed high. That is, the ordinary skilled artisan would have been able to understand the methods and compositions of the present invention useful for interfering with protein-protein interactions, such as the use of metal chelating compounds. Applicants direct the Examiner's attention to pages 1-3 of the instant specification, which includes references to journal articles published prior to the filing date of the present application. These references describe the use of metal chelating compounds to disrupt or prevent protein-

protein interactions, describe the biology of angiogenesis (including blood vessel growth, neointima formation, and physiological events involved in restenosis), describe the biology surrounding FGF1 and IL-1α production and effect, and generally demonstrate that the state of the art at the time of filing of the present application was sufficiently developed such that the ordinary skilled artisan – when armed with the disclosure set forth in the present application – would understand the compositions and methods useful in the presently claimed methods.

The Examiner is of the opinion that the U.S. Provisional Patent Application No. 60/314,837, to which priority is claimed, does not show that the Applicants are in possession of the claimed invention. However, Applicants point out that support for the claimed methods of inhibiting angiogenesis, neointima formation, inhibiting macrophage infiltration, inhibiting inflammation, inhibiting vascular cell proliferation, and inhibiting extracellular matrix secretion are indeed disclosed in the provisional patent application to which priority is claimed.

In particular, Applicants direct the Examiner's attention to page 1 of the provisional patent application, which sets forth that copper is involved in the promotion of angiogenic and inflammatory events in vivo. As known in the art at the time of filing, angiogenic events include neointima formation, vascular cell proliferation, and secretion of extracellular matrix. Also as known in the art at the time of filing, inflammatory events include the infiltration of macrophages to the site of vessel injury in a mammal.

Page 1 of the provisional application sets forth that copper chelators, such as tetrathiomolybdate (TTM), have the ability to limit the release of proinflammatory- and angiogenic cytokines. On page 7 of the provisional application, Applicants go on to state that mononuclear cells (known in the art to include "macrophages") are a rich source of FGF1, and are found at sites of inflammation along with IL-1α. Further, Applicants set forth on page 7 of the provisional application that IL-1α induces expression of vascular growth factors, and that IL-1α recruits mononuclear cells to a local site in or near vascular tissue. Further still, on page 7 of the provisional application, Applicants set forth that human tetrathiomolybdate therapy (i.e., "copper chelation") significantly reduces plasma levels of FGF and IL-1 species.

In determining the sufficiency of support in a disclosure with respect to the written description requirement, "it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him." *In re Edwards*, 196 USPQ 465, 467 (C.C.P.A. 1978) (citing *In re Lukach*, 169 USPQ 795 (C.C.P.A. 1971); *In re Driscoll*, 195 USPQ 434 (C.C.P.A. 1977)). More recently, in *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983), the Court of Appeals for the Federal Circuit, citing *In re Edwards*, emphasized:

> The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language. (Emphasis added).

In addition, in *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit pointed out that literal support is not required in order to satisfy the written description requirement:

> If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met. For example, in *Ralston Purina Co. v. Far-Mor-Co., Inc.*, 227 USPQ 177, 180 (Fed. Cir. 1985), the trial court admitted expert testimony about known industry standards regarding temperature and pressure in "the art of both farinaceous and proteinaceous vegetable materials." The effect of the testimony was to expand the breadth of the actual written description since it was apparent that the inventor possessed such knowledge of industry standards of temperature and pressure at the time the original application was filed. (Emphasis added).

Therefore, it is clear that the invention need not be described in *ipsis verbis*, *i.e.*, literally, for purposes of the written description requirement under 35 U.S.C. §112, first paragraph. Rather, what is needed is that the skilled artisan understand, based upon the disclosure in the specification as filed and the knowledge imputed to the skilled artisan at the time the specification was filed, that the inventor had possession of the claimed subject matter.

Applicants respectfully submit that, because of the written description in the provisional application 60/314,837 pertaining to the presently-claimed methods of inhibiting angiogenesis, inhibiting neointima formation, inhibiting macrophage

infiltration, inhibiting inflammation, inhibiting vascular cell proliferation, and inhibiting extracellular matrix secretion, the provisional application makes clear to the skilled artisan that removal, depletion and/or masking of Cu^{2+} is one way to prevent or inhibit angiogenesis, neointima formation, macrophage infiltration, inflammation, vascular cell proliferation, or extracellular matrix secretion. Because of the extensive teachings in the provisional application, in view of the level of skill in the art, Applicants submit that it not necessary to literally disclose each and every minute detail of the presently claimed invention, much less every known method of inhibiting or preventing the conditions or events identified in the present application, in order to satisfy the written description requirement.

Furthermore, Applicants respectfully submit that the provisional patent application also enables the presently-claimed invention beyond that which is required under 35 U.S.C. § 112, first paragraph.

The Examiner alleges that the presently-claimed invention is not sufficiently disclosed in the provisional application such that the presently-claimed invention is adequately enabled. However, the Examiner has not provided any details as to the basis of the allegation that the claimed invention is not adequately enabled. Assuming, *arguendo*, that the Examiner takes issue with the fact that Applicants do not disclose in the provisional application a separate experimental example describing in detail the subject matter of each of the presently-pending claims, Applicants respectfully traverse the Examiner's rejection for the following reasons. As Applicants have set forth above, the instant specification provides abundant guidance to the skilled artisan to practice the claimed invention.

It is well-settled that the invention need not contain a single example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation (*In re Borkowski*, 422 F.2d at 908), and "representative samples are not required by the statute and are not an end in themselves" (*In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970)). Thus, 35 U.S.C. § 112, first paragraph, enablement does not require any working examples. Nonetheless, Applicants have provided multiple examples in the provisional application.

For example, Applicants demonstrate, as set forth on pages 6 and 7 of the provisional application, that copper is required for the release of IL-1α into the extracellular compartment, where IL-1α acts as a chemoattractant for cells involved in inflammatory and angiogenic activities, and further, serves to induce expression of angiogenic molecules in endothelial cells. The provisional application goes on to state that removal of copper from a cell or extracellular location can inhibit the export of IL-1α and FGF1 into the extracellular area, and therefore, that chelation or sequestration of copper can be used to treat conditions associated with inflammatory and angiogenic activities. This is because, as Applicants set forth in the provisional application, inhibition of the copper-mediated release of IL-1α into the extracellular compartment will prevent IL-1α from acting as a chemoattractant for molecules involved in inflammatory and angiogenic activities, and will prevent the induction of expression of angiogenic molecules in endothelial cells.

Accordingly, as Applicants claim in the present invention, the provisional application discloses methods of inhibiting events associated with angiogenesis and/or inflammation in a mammal, including adventitial angiogenesis (claim 13), neointimal thickening or formation (claims 12 and 6, respectively), deposition of extracellular matrix (claim 11), cell proliferation associated with arterial wall injury (claims 9 and 10), and macrophage infiltration associated with vessel injury (claims 7 and 8).

Applicants further direct the Examiner's attention to MPEP § 2164.02, which states, in relevant part:

> Compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed. An example may be "working" or "prophetic." A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

Thus, either a working example or a prophetic example would satisfy the enablement requirement under 35 U.S.C § 112, first paragraph. Applicants direct the Examiner's attention to pages 6-7 of the provisional application, as described in detail above. It is respectfully submitted that the specification enables the claimed invention.

Furthermore, Applicants contend that the in vitro examples and data in the provisional application support the in vivo claims in the present application. As set forth

in detail above, it was well-known in the art at the time of filing that metal chelating compounds can be used in vivo to disrupt or prevent protein-protein interactions, that the biology of angiogenesis is well-characterized (including blood vessel growth, neointima formation, and physiological events involved in macrophage biology), that the biology surrounding FGF1 and IL-1α production and effect is well-characterized, and generally, that the state of the art at the time of filing of the present application was sufficiently developed such that the ordinary skilled artisan – when armed with the disclosure set forth in the present application – would understand the compositions and methods useful in the presently claimed methods.

Applicants remind the Examiner's that MPEP § 2164.02 states, in relevant part, that "[I]f the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Furthermore, this section of the MPEP requires that that the Examiner provide reasons for the alleged lack of enablement. Applicants respectfully submit that the Examiner has not met this burden in the present rejection of Applicants' priority claim.

Applicants respectfully submit that the provisional application more than adequately describes the presently-claimed invention in sufficient detail that one skilled in the art can reasonably conclude that Applicants had possession of the claimed invention, and enabled the claimed invention, at the time of filing. MPEP § 2163, citing, *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116. Accordingly, Applicants respectfully submit that the Examiner's rejection of Applicants' priority claim – based on an alleged lack of written description and enablement – does not apply, and as such, the present application is properly entitled to the priority claim to U.S. Provisional Patent Application No. 60/314,837, filed on August 24, 2001. Applicants request that the rejection of the priority claim be reconsidered and withdrawn.

Specification

The Examiner has objected to the use of the trademarked name "SPRAGUE-DAWLEY" without proper capitalization and generic reference in the

specification. Applications have amended the specification to ensure that "SPRAGUE-DAWLEY" is properly capitalized and referenced in the specification, and therefore, submit that the Examiner's objection has been overcome.

Applicants have also corrected the spelling of the term "tetrathiomolybdate" on page 5 of the specification as pointed out by the Examiner.

Finally, Applicants submit herewith a substitute specification to correct the inadvertent omission of the Greek letter "α" from the recitation of the term IL-1α in various instances throughout the specification. Applicants note that the Examiner has correctly identified this clerical error, which resulted from computer software issues while printing the as-filed specification. No new matter has been added by way of the submission of the substitute specification.

Rejection of claims 6 and 9 pursuant to 35 U.S.C. § 112, second paragraph

Claims 6 and 9 were separately rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention.

In the Examiner's view, the term "said mammal" in claim 9 does not have sufficient antecedent basis. Applicants have amended claim 9 to recite "the mammal." Accordingly, Applicants submit that the Examiner's rejection of claim 9 for indefiniteness has been overcome, and request reconsideration and withdrawal of the rejection.

In the Examiner's view, claim 6 fails to particularly point out and distinctly claim the subject matter Applicants regard as the invention. While not necessarily agreeing with the Examiner's rejection, but in an attempt to expedite prosecution of this application, Applicants have amended claim 6 to indicate that the claimed method of inhibition is inhibition of the "non-traditional" IL-1α export. Support for this amendment can be found in the specification, from line 20 through line 26 on page 34 of the application, which sets forth that "non-traditional export" is protein export that is not mediated by the endoplasmic reticulum-Golgi protein export mechanism.

The Examiner also alleges that the claim language, "an IL-1α release inhibiting amount of a copper chelator" is indefinite. Applicants respectfully disagree

with the Examiner's assertion. Applicants in fact define this amount of a copper chelator as an amount sufficient to detectably decrease the level of bioavailable copper in a cell such that there is a detectable decrease in the level of export of IL-1α release from the cell in response to stress (*See* page 35 of the specification, from line 21 through line 33).

Furthermore, Applicants provide direct and abundant guidance as to the metes and bounds of claim 6 in Experimental Example 2, at lines 22-23 on page 48 of the specification, regarding "an IL-1α release inhibiting amount of a copper chelator." Specifically, Applicants describe the administration of tetrathiomolybdate at a level of 10 mg/kg to rats, with no adverse side effects. Furthermore, as Applicants have described in detail elsewhere herein, there is extensive and detailed knowledge in the art related to the use and administration of copper chelators to mammals, including humans.

Applicants note that the Examiner's allegation that the claim encompasses administration of a "toxic amount" of a copper chelator "resulting in death" is clearly in direct contrast to the claimed invention. This is because the effective amount of a copper chelator – as described in detail above – necessarily relies upon the continued viability of the mammal in order to asses whether or not the administration inhibits neointima formation.

Applicants remind the Examiner that MPEP § 2173.04 states:

> Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). If the scope of the subject matter embraced by the claims is clear, and if applicants have not otherwise indicated that they intend the invention to be of a scope different from that defined in the claims, then the claims comply with 35 U.S.C. 112, second paragraph.

Applicants submit that the subject matter embraced by claim 6 is indeed clear, as it is defined in the specification as described above.

Furthermore, Applicants remind the Examiner that Applicants are entitled to be their own lexicographer for the purpose of the instant patent application. In this regard, MPEP § 2111.01 states, in relevant part:

> Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. Toro Co. v. White Consolidated Industries Inc., 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999) (meaning of words used in a claim is not construed in a "lexicographic vacuum, but in the context of the specification and drawings").

Again, Applicants submit that the subject matter embraced by claim 6 is indeed clear, as it is defined in the specification, as described above.

Accordingly, Applicants respectfully submit that claim 6 and amended claim 9 are not indefinite, and request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. § 102(e)(1)

Claims 6-9 and 11-13 were rejected under 35 U.S.C. § 102(e)(2) as being anticipated by U.S. Patent No. 6,951,890 ("the '890 patent"). Specifically, it is the Examiner's view that the cited reference teaches the presently claimed invention. Applicants respectfully submit that claims 6-9 and 11-13, including amendments set forth herein, are not anticipated by under 35 U.S.C. § 102(e)(2) by the '890 patent for the following reasons.

35 U.S.C. § 102(e)(2) provides that:

> A person shall be entitled to a patent unless –
> (e) the invention was described in — [...](2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent[.]

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting Verdegaal Bros. v. Union Oil Co. of Calif., 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." Id. (quoting Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, when taken alone, the '890 patent must describe each and every element of each of present claims 6-9 and 11-13 in order to anticipate the claims under 35 U.S.C. § 102(e)(2). However, the '890 patent does not meet this burden.

Applicants contend that the Examiner's rejection under 35 U.S.C. § 102(e)(2) does not apply, because the presently-pending claims are indeed entitled to the benefit of U.S. Provisional Patent Application No. 60/314,837, filed on August 24, 2001, as set forth in detail above in response to the rejection of the priority claim. Because the patent application which serves as the basis for the '890 patent was not filed prior to

Applicants' earliest priority date, the '890 patent is not a proper anticipatory reference under 35 U.S.C. § 102(e)(2), and the Examiner's rejection in this regard is therefore moot.

Despite the fact that the '890 patent is not a proper anticipatory reference under 35 U.S.C. § 102(e)(2), the '890 patent could not in any event not be considered to anticipate Applicants' presently-claimed invention, for the following reasons.

As noted by the Examiner, Applicants' presently-claimed invention encompasses methods of inhibiting neointima formation or thickening, inhibiting macrophage infiltration, inhibiting cell proliferation, inhibiting secretion of extracellular matrix, and inhibiting adventitial angiogenesis. The '890 patent does not teach any of these claimed elements.

The '890 patent teachings fall well short of the present invention. The '890 patent teaches, among other things, *migration* of *stem cells* to a site of vascular injury and repair of tissue damage by way of stem cell responses (column 27, lines 25-34), treatment of ulcers (column 27, lines 18-23), mediation of leukocyte adhesion by *mediation of expression of cell-adhesion molecules* (column 13, lines 11-24), and the general notion that inflammation can be associated with cardiovascular events in diabetic patients (column 8, lines 25-30). All of these teachings are found in the background of the invention set forth in the '890 patent, and none of these teachings – when taken alone or in combination with one another – rise to the level of Applicants' presently-claimed invention.

Therefore, the '890 patent does not teach the entirety of Applicants' presently-claimed invention. More specifically, the '890 patent does not teach "each and every element" of Applicants' presently-claimed invention, as required under 35 U.S.C. § 102(e)(2). Accordingly, Applicants respectfully submit that amended claims 6-9 and 11-13 are not anticipated under 35 U.S.C. § 102(e)(2), and respectfully request reconsideration and withdrawal of the rejection.

Rejection of claims 9 and 10 under 35 U.S.C. § 103(a)

Claims 9 and 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable in view of the '890 patent, further in view of Medford et al. (U.S. Patent No. 5,877,203; Hereinafter, "the '203 patent"). It is the Examiner's view that the '890 patent discloses, among other things, *migration* of *stem cells* to a site of vascular injury and repair of tissue damage by way of stem cell responses (column 27, lines 25-34), treatment of ulcers (column 27, lines 18-23), mediation of leukocyte adhesion by *mediation of expression of cell-adhesion molecules* (column 13, lines 11-24), and the general notion that inflammation can be associated with cardiovascular events in diabetic patients (column 8, lines 25-30). It is further the Examiner's view that The '203 patent teaches the administration of compounds that are "known to chelate metals," and that the combination of the references renders obvious Applicants' presently claimed invention. Applicants respectfully disagree, and traverse the rejection for the following reasons.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here, and therefore, Applicants respectfully submit that the Examiner has not met her burden with respect to the establishment of a *prima facie* case of obviousness.

Applicants contend that the Examiner's rejection under 35 U.S.C. § 103(a) does not apply, because the presently-pending claims are indeed entitled to the benefit of U.S. Provisional Patent Application No. 60/314,837, filed on August 24, 2001, as set forth in detail above in response to the rejection of the priority claim. Because the patent application which serves as the basis for the '890 patent was not filed prior to Applicants' earliest priority date, the '890 patent is not a proper reference for the consideration of

obviousness under 35 U.S.C. § 103(a), regardless of whether the '890 patent is viewed in combination with the '203 patent, and the Examiner's obviousness rejection is therefore moot.

Despite the fact that the '890 patent, taken in view of the '203 patent, is not a proper reference for the purpose of obviousness under 35 U.S.C. § 103(a), the combination of the '890 patent with the '203 patent could not in any event not be considered to render obvious Applicants' presently-claimed invention for the following reasons.

As noted by the Examiner, Applicants' presently-claimed invention encompasses methods of inhibiting neointima formation or thickening, inhibiting macrophage infiltration, inhibiting cell proliferation, inhibiting secretion of extracellular matrix, and inhibiting adventitial angiogenesis. Neither the '890 patent, the '203 patent, nor the combination of the two patents cited by the Examiner teaches any of these claimed elements.

The '890 patent teachings fall well short of the present invention. The '890 patent teaches, among other things, *migration* of *stem cells* to a site of vascular injury and repair of tissue damage by way of stem cell responses (column 27, lines 25-34), treatment of ulcers (column 27, lines 18-23), mediation of leukocyte adhesion by *mediation of expression of cell-adhesion molecules* (column 13, lines 11-24), and the general notion that inflammation can be associated with cardiovascular events in diabetic patients (column 8, lines 25-30). All of these teachings are found in the background of the invention set forth in the '890 patent, and none of these teachings – when taken alone or in combination with one another – rise to the level of Applicants' presently-claimed invention.

The '203 patent does not remedy this deficiency. The Examiner alleges that the '203 patent (in particular, the abstract) teaches that dithiocarboxylates and dithiocarbamates are "well known metal chelators." Applicants respectfully contend that the '203 patent presents no such teaching in the abstract. The '203 patent teaches – in the background of the invention – that dithiocarbamates are useful for heavy metal detoxification, and additionally, as enzyme inhibitors (eg., dehydrogenase inhibitor) (*See* column 2). Experimental Example 1 in the '203 patent teaches that a dithiocarbamate can

be used to block expression of certain cell adhesion molecule genes in endothelial cells. Nowhere does the '203 patent teach the inhibition of the proliferation of cells as a result of cell wall injury, as set forth in Applicants' claims 9 and 10.

Therefore, because neither the '890 patent nor the '203 patent discloses Applicants' presently-claimed invention, and because neither reference provides any motivation or suggestion to arrive at Applicants' presently-claimed invention, the '890 patent and the '203 patent, when taken together, do not provide any suggestion or motivation to the skilled artisan to arrive at Applicants' presently-claimed invention. Furthermore, because the '890 patent and the '203 patent, when taken together, do not provide any suggestion or motivation to the skilled artisan to arrive at Applicants' presently-claimed invention, the skilled artisan would not have any reasonable expectation of success in arriving at the invention set forth in claims 9 and 10.

For the reasons discussed above, because the presently-pending claims are entitled to the benefit of U.S. Provisional Patent Application No. 60/314,837, filed on August 24, 2001, as set forth in detail above in response to the rejection of the priority claim, the combination of '890 patent and the '203 patent cannot render claims 9 and 10 *prima facie* obvious under 35 U.S.C. § 103(a) and, therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

Summary

Applicants respectfully submit that the pending claims, including the amended claims, are fully supported in the specification as filed, and that no new matter has been added by way of the present Amendment and Response.

Favorable examination and allowance of the claims is hereby requested.

Respectfully submitted,

THOMAS MACIAG, et al.

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